

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Berzofsky et al.

Application No. 10/532,374

Filed: April 21, 2005

Confirmation No. 4276

For: METHODS TO PREVENT TUMOR
RECURRENCE BY BLOCKADE OF TGF-
BETA

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Examiner: Sheela J. Huff

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UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION OF DR. JAY A. BERZOFSKY UNDER 37 C.F.R. § 1.132

I, Jay A. Berzofsky, M.D., Ph.D declare as follows:

1. I am named as co-inventor of U.S. Patent Application No. 10/532,374, filed April 21, 2005. I have read the above-referenced patent application and the Office action dated November 8, 2007.

2. A copy of my *curriculum vitae* is attached hereto as **Exhibit A**. At present, I hold a position as Chief of the Vaccine Branch, Center for Cancer Research, at the National Cancer Institute. I have had 33 years of experience in research including work on immunology and biochemistry, vaccines and cancer. I have published over 420 scientific articles in scientific journals and books. I was president of the American Society for Clinical Investigation from 1993-1994, and have been Chair of the Medical Sciences Section of the American Association for the Advancement of Science from 2007-2008. By virtue of my education, training, and professional experience, I am knowledgeable about the biology and treatment of tumors.

3. I understand that the Examiner has rejected the claims of the application for allegedly being obvious over Dasch *et al.* (U.S. Patent No. 6,090,383) in view of Barbera-Guillem (U.S.

Patent No. 6,224,866), Rosenblum (U.S. Patent Application No. 2005/0214307), and Zavada *et al.* (U.S. Patent No. 6,297,041) because the combination of references teach “that compounds that treat tumors can also be used to treat tumor recurrence” (Office action at page 5). However, the claimed invention is not directed to *treatment* of recurrence of a tumor. Instead, the claimed invention is directed to *inhibiting* recurrence of a tumor. As discussed below, the effectiveness of an agent on a tumor cell in one stage of the disease does not predict the effectiveness of the same agent on a tumor cell in a different stage of the disease. Thus, it would not be obvious that an agent effective at treating a recurrence of a tumor also would be effective at inhibiting a recurrence.

4. Before discussing the distinctions between inhibition and treatment of tumors, general comments regarding tumors are provided in this paragraph. It is my experience, as a researcher in the subject of tumor biology and treatment, that there are recognized biological differences between original (primary) tumors, recurrent tumors, and metastatic (secondary) tumors. Specifically, a tumor recurrence is the return of a tumor, at the same site as the original (primary) tumor, after the tumor has been removed surgically, by drug or other treatment, or has otherwise disappeared. A tumor recurrence is not a metastasis, as a metastasis is the spread of a tumor from one part of the body to another. Tumors formed from cells that have spread are called “secondary tumors” and contain cells that are like (but not always identical to) those in the original (primary) tumor. There can be a recurrence of either a primary tumor or a metastasis. Cells of a recurrent primary tumor or a recurrent metastatic tumor can arise by escape from anti-tumor immune responses and differ from the original primary tumor by having loss of a tumor antigen, mutation of a tumor antigen, or loss or decreased expression of Major Histocompatibility Complex (MHC) molecules presenting the tumor antigens. Tumors that recur after chemotherapy usually do so by development of mutations or other changes resulting in resistance to the chemotherapy agent used.

5. Inhibiting (or preventing) the occurrence of a tumor is very different from treating it after it occurs. Thus, a distinction must be made between *treatment* and *inhibition* of a tumor. Because of the immunological and physiological differences between the cells of primary (or secondary) tumors and the cells of recurrent tumors, not all treatments that effectively cause

regression of a primary tumor will be effective at subsequently inhibiting a recurrent tumor. For example, pediatric sarcomas, such as Ewing's sarcoma or Alveolar Rhabdomyosarcoma, can both be treated successfully with chemotherapy to cause a complete remission in most cases, but the treatments are ineffective at inhibiting the recurrence of the tumors in most patients, even if the chemotherapeutic agents are effective at treating the recurrence itself (see Pizzo and Poplack (eds.), *Management of Common Cancers of Childhood*, page 1006, right column, 2002, 4th Ed, Lippincott Williams & Wilkins, Philadelphia, PA; Rodriguez-Galindo *et al*, *Cancer*, 94: 561-569, 2002). Thus, the characteristics of a recurrent primary tumor (or recurrent metastatic tumor) are very different from the original primary tumor (or original metastatic tumor), despite the fact that the recurrent tumor exists at the site of the original tumor. In general, it is my experience that inducing the regression of (treating) a primary or secondary tumor is very different from inhibiting recurrence of a tumor, as the former reduces the size of an established tumor and the latter prevents the return of a variant form of a tumor.

6. Furthermore, treating a primary tumor or a metastasis is very different from treating a recurrence of the primary tumor or the metastasis. It is very well known by those who treat cancer patients that not all agents used to treat a primary tumor will be effective at treating a recurrence of the tumor because cells of a recurrent tumor are variants of the cells in the original tumor and differ immunologically from the original primary tumor. Similarly, recurrent metastases can differ from the original metastases by being escape variants. Thus, while Zavada *et al*. and Rosenblum disclose that some agents that can treat a primary tumor may possibly be used to treat a recurrent tumor, in the vast majority of cases a tumor that recurs during or after a primary treatment is an escape variant that is resistant to the original therapeutic agent. Therefore, one of skill in the art would expect that the agent used to treat the primary tumor could neither prevent nor treat the recurrent tumor. Furthermore, once a tumor recurs, it is rarely curable, so there are few agents that can successfully treat such recurrent tumors. Consequently, because of biological differences between a primary or secondary tumor and a recurrence, the agent used to treat a recurrence can be different than the agent used to treat the original tumor.

7. The distinction between treatment and inhibition is most recently exemplified by the prophylactic Human Papillomavirus (HPV) vaccine, which prevents HPV infection and cervical

cancer. However, the vaccine cannot treat HPV infection once it occurs and it cannot treat or prevent a recurrence of HPV infection in someone already infected (Frazer *et al.*, *Eur. J. Immunol.*, 37:S148-155, 2007; Hildesheim *et al.*, *JAMA*, 298:743-753, 2007). Further, it cannot treat cervical cancer once it occurs. Thus, there is a clear distinction in the activity of the vaccine between *inhibiting* HPV infection or cervical cancer, and *treating* HPV infection or cervical cancer.

8. I further believe that not all agents used to treat a recurrence will be effective at inhibiting a recurrence. A representative example of a situation in which an agent that can treat recurrence cannot be used to prevent recurrence is in non-small cell lung cancer (NSCLC). Chemotherapy, usually a platinum-based doublet regimen (cisplatin or carboplatin administered with a paclitaxel, docetaxel, or gencitabine) is the standard of care for the treatment of locally advanced stage and metastatic NSCLC (Schiller *et al.*, *N Engl J Med.*, 346:92-98, 2002). In patients with inoperable recurrent local-regionally advanced (stage III) NSCLC, platinum doublet chemotherapy combined with radiation can result in 5-year disease-free survivals of 15-20% compared to 5-6% for treatment with radiation alone, which used to be the standard treatment (Dillman *et al.*, *J Natl Cancer Inst.*, 88:1210-1215, 1996; Belani *et al.*, *J Clin Oncol.*, 23:3760-3767, 2005). However, the same platinum-based doublet therapy was found in large clinical trials not to be effective in preventing recurrences or prolonging overall survival or disease-free survival when used in early stage IB NSCLC as “adjuvant therapy” after surgery to prevent recurrence of the tumor (Wakelee *et al.*, *Clin Lung Cancer*, 8:18-21, 2006). Thus, one of skill in the art would conclude from this example that therapies that are beneficial in treating recurrent tumors are not necessarily effective in preventing recurrence after treatment of the disease with primary therapy like surgery.¹

9. In summary, based on my education, training, and professional experience, I believe that it would not be obvious to one of skill in the art that an agent effective at treating a tumor recurrence also would be effective at inhibiting (preventing) a recurrence.

¹ Citations in this paragraph were provided to me by my colleague, Dr. John Morris, Co-Director of the Clinical Trials Team, Metabolism Branch, Center for Cancer Research, NCI.

10. All statements made herein and of my own knowledge are true and all statements made on information are believed to be true; and further, these statements were made with the knowledge that willful false statements and like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements made may jeopardize the validity of the application or any patent issuing thereon.

Date March 10, 2008


Jay A. Berzofsky, M.D., Ph.D.